form. The official action of June 17, 2002, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to certain novel non-hemolytic cytotoxic peptides having a selective cytolytic activity such that there are much more toxic to pathogenic cells then there are to red blood cells. The peptide may be a cyclic derivative of a peptide having a net positive charge that is greater than +1 and comprising both L-amino acid residues and D-amino acid residues, or comprising only D-amino acid residues and having an α-helix breaker moiety. The peptide may also comprise both L-amino acid residues and D-amino acid residues, having a net positive charge which is greater than +1, and having a sequence of amino acid such that the same amino acid sequence in which each residue is in the L-configuration is not found in nature, and cyclic derivatives thereof. The peptides may also be a random copolymer consisting of a hydrophobic, a positively charged, and a D-amino acid. The claims exclude the peptides of SEQ ID NO:1.

Claims 1-14, 20, 21 and 27-33 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that claim 1(B) recites "a corresponding amino acid sequence comprising only L-amino acid residues is

not found in nature". The examiner questions what is meant by "corresponding". This part of the rejection is respectfully traversed.

Claim 1(B) has now been amended to clarify the meaning. This does, indeed, mean that the two peptides are absolutely identical in all respects other than the stereochemistry of the α carbon. Accordingly, this part of the rejection has now been obviated.

The examiner states that claim 14 is not properly dependent on claim 1, as claim 1 excludes all peptides which consist solely of L-amino acids. This part of the rejection is respectfully traversed.

In applicants' amendment of March 19, 2002, the underlines in peptide 95, which had appeared in claim 14 as originally filed, were inadvertently omitted. Claim 14 has now been amended to correct this error. Furthermore, it is noted that the sequence listing erroneously states that sequence 95 is all L-amino acid. Accordingly, the sequence listing has also now been corrected. Attached hereto is a substitute page 107 of the sequence listing correcting this error. Furthermore, attached hereto is a 3½ disk containing the sequence listing in computer readable form in accordance with 37 C.F.R. §1.821(e).

The following statement is provided to meet the requirements of 37 C.F.R. §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.821(f), that the content of the Sequence Listing paper copy submitted on June 15, 2000, after substitution of attached page 107, and the computer readable copy of the sequence listing are believed to be the same.

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendment included in substitute page 107 of the sequence listing is believed to be supported in the application as filed and that substitute page 107 of the sequence listing is not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is the same as Sequence Listing paper copy submitted on June 15, 2000, after substitution of attached page 107.

The examiner states that claim 31 recites inhibition of a "viral activity", but it is not understood which activities are intended.

Claim 31 has now been amended to delete the term "effective to inhibit a viral activity" and to substitute that the amount is "an antiviral effective amount". The term "antiviral" means "destroying viruses or suppressing their

replication" as defined, for example, in Dorland's Illustrated Medical Dictionary, 29th Ed., 2001, p. 107 (copy attached).

Accordingly, it is submitted that the entire rejection under 35 U.S.C. §112, second paragraph, has now been obviated. Reconsideration and withdrawal thereof are respectfully urged.

Claim 1 has been rejected under 35 U.S.C. §102(b) as being anticipated by Shai. The examiner states that Shai teaches that the peptide designated "$(D)P^7L^{18}L^{19}$" is antibacterial but non-hemolytic. This rejection is respectfully traversed.

The examiner is correct that we had misidentified this peptide in the previous response as being the peptide 16 of the present application. The peptide of the present application corresponding to the peptide $(D)P^7L^{18}L^{19}$, described by Shai, is the peptide of SEQ ID NO:1. Claim 1 has now been amended to insert a proviso excluding this peptide. If a specification contains a written description of a genus and numerous species within that genus, it necessarily contains a written description of that genus minus one of the specifically disclosed species. See *In re Johnson*, 194 USPQ 187, 196 (1977). Accordingly, claim 1 is no longer anticipated by Shai. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1, 2, 7-11, 20 and 34 have been rejected under 35 U.S.C. §103 as being unpatentable over Maloy. The examiner states that Maloy teaches cytolytic peptides containing D-amino acids. The examiner states that applicants have argued that for each of the disclosed peptides, if one were to replace each of the D-amino acids with L-amino acids, the results would be a peptide that is found in nature. The examiner finds this unpersuasive as Maloy includes peptides that are not found in nature. Further, the examiner considers the peptides of Maloy to be random copolymers as defined in part (C) of claim 1. This rejection is respectfully traversed.

Claim 1(B) requires that the peptide comprise both L-amino acid residues and D-amino acid residues. While this definition has other requirements, it is only necessary to consider this first requirement as Maloy teaches no peptides having both L-amino acid residues and D-amino acid residues. Note the first sentence of the abstract of Maloy, which reads:

> Biologically active analogs of magainin peptides wherein each amino acid residue of the peptide is a D-amino acid residue or a glycine reside.

Glycine residues are neither D nor L. Thus, it is apparent that none of the analogs of Maloy include any L-amino acid residues. Thus, they are enantiomers and not diastereomers, as are the peptides of the present application. Accordingly,

whether or not the corresponding peptides with L-amino acids are found in nature, none of the analogs of Maloy fall within the scope of claim 1(B) as none have both L-amino acid residues and D-amino acid residues.

As to sub-paragraph (C) of claim 1, the random copolymer contains a long chain of amino acid residues, each of which are one of three different residues: a hydrophobic residue; a positively-charged residue; and a D-amino acid residue. At any given position, the residue may be randomly selected from the three specified residues. It is not believed that any of the peptides of Maloy can be considered to be a random polymer which is a random mixture of three amino acids, one being hydrophobic, one being positively-charged, and the other being a D-amino acid.

The examiner refers to the peptides disclosed in column 8, line 28+. However, none of these are copolymers of three amino acid residues. The present claim 1(C) does not read on a copolymer of ser, lys, ala and phe. Accordingly, this part of claim 1 is not anticipated by Maloy as well. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all the claims now present in the specification clearly define over the references of record

and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Specification

Page 107 of the sequence listing has been replaced.

In the Claims

1 (~~Thrice~~Four-Times-Amended). A non-hemolytic cytolytic peptide having a selective cytolytic activity manifested in that it has a cytolytic activity on pathogenic cells, said pathogenic cells being cells which are non-naturally occurring within the body consisting of microbial pathogenic organisms and malignant cells; and it is non-hemolytic, namely it has no cytolytic effect on red blood cells or has a cytolytic effect on red blood cells at concentrations which are substantially higher than that in which it manifests said cytolytic activity on pathogenic cells, said non-hemolytic cytolytic peptide being selected from the group consisting of:

(A) a cyclic derivative of a peptide having a net positive charge which is greater than +1, and comprising both L-amino acid residues and D-amino acid residues, or comprising only D-amino acid residues, and comprising an α-helix breaker moiety;

(B) a peptide comprising both L-amino acid residues and D-amino acid residues, having a net positive charge which is greater than +1, and having a sequence of amino acids

such that ~~a corresponding~~the same amino acid sequence ~~comprising only L-amino acid residues~~in which each residue is in the L-configuration is not found in nature, and cyclic derivatives thereof; and

(C) a random copolymer consisting of a hydrophobic, a positively charged and a D-amino acid, with the proviso that the peptide is not that of SEQ ID NO:1.

14 (~~Four Times~~Five-Times-Amended). A cyclic derivative of a non-natural synthetic peptide according to claim 7, selected from the group of peptides consisting of those herein designated 92-95 (SEQ ID NOS:92-95, respectively), of the sequence:

92) Cyclic Cys Lys Leu **Leu** **Leu** Lys Leu Leu **Leu** Lys Leu Leu Lys Cys,

93) Cyclic Cys Lys Leu **Leu** **Leu** Lys Leu Lys **Leu** Lys **Leu** Lys Cys,

94) HN - Lys Leu **Leu** **Leu** Lys Leu Leu **Leu** Lys **Leu** Leu Lys - CO, and

~~**95)** HN - Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys - CO.~~

95) HN - Lys Leu **Leu** **Leu** Lys Leu Lys **Leu** Lys **Leu** Leu Lys - CO.

31 (~~Once~~Twice-Amended). A composition comprising a pharmaceutically acceptable carrier and a peptide according to

claim 1 in an anti-viral effective amount ~~effective to inhibit a viral activity~~.

32(~~New~~Amended). The composition of claim 31, wherein said ~~viral activity~~antiviral effective amount is an amount effective to inhibit viral-induced hemolysis.

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(ii) MOLECULE TYPE: peptide

(vii) IMMEDIATE SOURCE:
(B) CLONE: peptide 94

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:group(3, 4, 8, 10)
(D) OTHER INFORMATION:/product= "D-amino acid residues"

(ix) FEATURE:
(D) OTHER INFORMATION:/product= "OTHER"
/note= "cyclic peptide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(vii) IMMEDIATE SOURCE:
(B) CLONE: peptide 95

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION:group(3, 4, 8, 10)
(D) OTHER INFORMATION:/product= "D-amino acid residues"

(ix) FEATURE:
(D) OTHER INFORMATION:/product= "cyclic pepetide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(vii) IMMEDIATE SOURCE:
(B) CLONE: peptide 96 (monomer, peptide 23C)

an·ti·su·dor·if·i (an″tī-soo″dor-if′ik) [*anti-* + *sudorific*] 1. inhibiting perspiration. 2. an agent that inhibits perspiration.

an·ti·sym·pa·thet·ic (an″tī-sim″pə-thet′ik) sympatholytic.

an·ti·tem·plate (an″tī-tem′plāt) a hypothetical substance said to inhibit mitosis of normal cells and, on injury to cells, t diffuse out of the cells to initiate mitosis.

an·ti·te·tan·ic (an″tī-tə-tan′ik) preventing or curing tetanus.

an·ti·the·nar (an″tī-the′nar) [*anti-* + *thenar*] situated opposite to the palm or the sole.

an·ti·ther·mic (an″tī-thər′mik) [*anti-* + *thermic*] antipyretic (def. 1).

an·ti·throm·bin (an″tī-throm′bin) [*anti-* + *thrombin*] any naturally occurring or therapeutically administered substance that neutralizes the action of thrombin and thus limits or restricts blood coagulation. Six naturally occurring antithrombins have been designated by Roman numerals I to VI; antithrombins I and III are the most common and significant ones. Heparin is also considered an antithrombin.
a. I, fibrin; referring to the capacity of fibrin to adsorb large amounts of thrombin and thus neutralize (but not inactivate) it.
a. III, an α_2-globulin of the serpin family synthesized in the liver and found in plasma and various extravascular sites, which inactivates thrombin in a time-dependent irreversible reaction. It also inhibits certain other proteinases with serine active sites, including coagulation factors Xa, XIIa, XIa, and IXa, and kallikrein. Inherited deficiency of the protein, a rare autosomal dominant disorder, is associated with recurrent deep vein thrombosis and pulmonary emboli.

an·ti·throm·bo·plas·tin (an″tī-throm″bo-plas′tin) any agent or substance that prevents or interferes with the interaction of the blood coagulation factors as they generate prothrombinase.

an·ti·throm·bot·ic (an″tī-throm-bot′ik) 1. preventing or interfering with the formation of thrombi. 2. an agent that so acts; see also *anticoagulant* and *thrombolytic*.

an·ti·thy·roid (an″tī-thī′roid) counteracting the functioning of the thyroid, especially in its synthesis of thyroid hormones.

an·ti·thy·ro·tox·ic (an″tī-thī″ro-tok′sik) counteracting the toxic effects of excessive amounts of thyroid hormones.

an·ti·thy·ro·trop·ic (an″tī-thī″ro-trop′ik) inhibiting the secretion or actions of thyrotropin.

an·ti·t nic (an″tī-ton′ik) reducing tone or tonicity.

an·ti·tox·i (an″tī-tok′sik) 1. effective against a poison. 2. pertaining to antitoxin.

an·ti·tox·i·gen (an″tī-tok′sĭ-jən) antitoxinogen.

an·ti·t x·in (an″tī-tok′sin) 1. antibody against a toxin. 2. a purified antiserum from animals (usually horses) immunized by injections of a toxin or toxoid, administered as a passive immunizing agent to neutralize a specific bacterial toxin, e.g., botulinus, tetanus, or diphtheria.
botulinal a., botulinum a., botulinus a., botulism a.
botulism a. [USP], an equine antitoxin against the toxins produced by the type A, B, or E strain of *Clostridium botulinum*. Generally trivalent (ABE) antitoxin is used. Called also *botulinal a., botulinum a.*, and *botulinus a.*
bovine a., antitoxin containing antibodies derived from the cow instead of from the horse, for use on persons who are hypersensitive to horse serum.
***Clostridium perfrigens* types C and D a.**, an antitoxin prepared from serum of animals hyperimmunized with toxins of *C. perfrigens* types C and D, administered immediately after birth for prevention of enterotoxemia in calves, lambs, and suckling pigs.
diphtheria a. [USP], equine antitoxin against the toxin of *Corynebacterium diphtheriae*, used for treatment of diphtheria.
equine a., an antitoxin derived from the blood of healthy horses that have been immunized against a specific bacterial toxin.
gas gangrene a., a polyvalent equine antitoxin against toxins of *Clostridium* species causing gas gangrene, formerly administered for prevention or treatment of gas gangrene.
tetanus a. [USP], equine antitoxin against the toxins of *Clostridium tetani;* used for the passive prevention and treatment of tetanus. It is rarely used, tetanus immune globulin being preferred if available.
tetanus and gas gangrene a's, a combination of tetanus and gas gangrene antitoxins.

an·ti·tox·in·o·gen (an″tī-tok-sin′o-jen) [*antitoxin* + *-gen*] an antigen that stimulates the production of antitoxin, i.e., a toxin or toxoid.

an·ti·tox·i·num (an″tī-tok-sī′nəm) [L.] antitoxin.

an·ti·trag·i· us (an″tī-traj′ī-kəs) see under *musculus*.

an·ti·tra·gus (an″tī-tra′gəs) [*anti-* + *tragus*] [TA] a projection opposite the tragus, bounding the cavitas conchae posteroinferiorly and continuous above with the anthelix.

an·ti·tr p·o·ne·mal (an″tī-trep″o-ne′məl) 1. effective against *Treponema*. 2. an agent that is effective against *Treponema*.

an·ti·trich·o·mo·nal (an″tī-trik″o-mo′nəl) 1. effective against *Trichomonas*. 2. an agent that is destructive to *Trichomonas*.

an·ti·tris·mus (an″tī-triz′məs) a spasm that prevents the closure of the mouth.

an·ti·trope (an′tī-trōp) [*anti-* + Gr. *trepein* to turn] any organ that forms a symmetrical pair with another.

an·ti·trop·ic (an″tī-trop′ik) corresponding, but oppositely oriented, as a right and a left glove.

an·ti·tro·pin (an″tī-tro′pin) antiopsonin.

an·ti·try·pan·o·so·mal (an″tī-trī-pan″o-so′məl) 1. effective against trypanosomes. 2. a drug for combating trypanosomiasis.

α_1-an·ti·tryp·sin (an″tī-trip′sin) alpha$_1$-antitrypsin.

an·ti·tu·ber·cu·lin (an″tī-too-bər′ku-lin) an antibody developed following the injection of tuberculin.

an·ti·tu·ber·cu·lot·ic (an″tī-too-bər″ku-lot′ik) 1. therapeutically effective against tuberculosis; called also *antituberculous*. 2. an agent that is therapeutically effective against tuberculosis.

an·ti·tu·ber·cu·lous (an″tī-too-bər′ku-ləs) therapeutically effective against tuberculosis.

an·ti·tu·bu·lin (an″tī-too′bu-lin) an agent that prevents the polymerization of tubulin, and thus the formation of microtubules in a cell.

an·ti·tu·mor·i·gen·ic (an″tī-too″mər-ĭ-jen′ik) counteracting tumor formation.

an·ti·tus·sive (an″tī-tus′iv) 1. relieving or preventing cough. 2. an agent that relieves or prevents cough.

an·ti·ty·phoid (an″tī-tī′foid) counteracting or preventing typhoid.

an·ti·ul·cer·a·tive (an″te-ul′sər-ə″tiv) 1. preventing or promoting the healing of ulcers. 2. an agent that so acts.

an·ti·urat·ic (an″tī-u-rat′ik) preventing the deposit of urates.

an·ti·uro·lith·ic (an″tī-u″ro-lith′ik) 1. preventing the formation of urinary calculi. 2. an agent that prevents the formation of urinary calculi.

an·ti·vac·ci·na·tion·ist (an″tī-vak″sī-na′shən-ist) a person who is opposed to vaccination.

an·ti·ven·ene (an″tī-vē-nēn′) [*anti-* + L. *venenum* poison] antivenin.

an·ti·ven·in (an″tī-ven′in) [*anti-* + L. *venenum* poison] a proteinaceous material used in the treatment of poisoning by animal venom. See also *antivenomous serum*, under *serum*.
black widow spider a., a. *(Latrodectus mactans)*.
a. (Crotalidae) polyvalent [USP], a lyophilized preparation containing specific venom-neutralizing globulins obtained from the serum of horses immunized with the venoms of *Crotalus atrox* (western diamondback rattlesnake), *C. adamanteus* (eastern diamondback rattlesnake), *C. durissus terrificus* (tropical rattlesnake), and *Bothrops atrox* (fer-de-lance); used to neutralize the effects of envenomation by pit vipers native to North, Central, and South America.
a. *(Latrodectus mactans)* [USP], a lyophilized preparation containing specific venom-neutralizing globulins obtained from the serum of horses immunized with the venom of *Latrodectus mactans* (the black widow spider); occasionally used to treat the symptoms of black widow spider bites. Called also *black widow spider a.*
a. *(Micrurus fulvius)* [USP], a lyophilized preparation containing specific venom-neutralizing globulins obtained from the serum of horses immunized with the venom of *Micrurus fulvius* (the eastern coral snake); used to neutralize the effects of envenomation by the eastern coral snake *(M. fulvius fulvius)* and the Texas coral snake *(M. fulvius tenere)*. Called also *North American coral snake a.*
North American coral snake a., a. *(Micrurus fulvius)*.
polyvalent crotaline a., a. (Crotalidae) polyvalent.

an·ti·ven·om (an″tī-ven′om) antivenin.

an·ti·ven·om·ous (an″tī-ven′ə-məs) counteracting venom.

An·ti·vert (an′tī-vert″) trademark for a preparation of meclizine hydrochloride.

an·ti·vi·ral (an″tī-vī′rəl) 1. destroying viruses or suppressing their replication. 2. an agent that destroys viruses or suppresses their replication.

an·ti·vi·rot·ic (an″tī-vī-rot′ik) antiviral.

an·ti·vi·ta·min (an″tī-vī′tə-min) a substance that interferes with the synthesis or metabolism of a vitamin.

an·ti·vivi·sec·ti n (an″tī-viv″ĭ-sek′shən) opp sition to vivisection.